REMARKS

Courtesies extended to Applicants' representative Lisa A. Haile in a telephone interview on August 29, 2001 are acknowledged with appreciation. Claims 64 to 136 are pending and under consideration. In the present communication, claims 64, 104, 123 and 124 have been amended. A marked up version to show changes made is attached herewith as Exhibit A. The claims as they would stand upon entry of the amendments is attached herewith as Exhibit B.

The amendments submitted herewith are supported by the specification and original claims and do not add new matter. The amendments do not require a new search or raise new issues for consideration because they merely address issues already raised by the Examiner or define Applicants' invention more clearly. It is submitted that the amendments place the claims in condition for allowance or in better condition for appeal by reducing the number of issues for consideration on appeal. The amendments were not made earlier in the prosecution because it is maintained that the previously pending claims were allowable. Since the amendments do not add new matter or require a new search or consideration, and place the claims in condition for allowance or in better condition for appeal, entry of the amendments is respectfully requested.

Claim Rejection Under 35 U.S.C. § 112, first paragraph

The rejection of claims 64 to 94 and 104 to 134 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, is respectfully traversed.

Applicants invention, as defined by claims 64 and 104, and claims dependent therefrom, recites a non-invasive method for obtaining a skin sample for use in isolating or detecting a nucleic acid in a skin sample. The method includes applying an adhesive to the skin or scraping the skin such that the adhesive or scraped skin sample contains nucleic acid from the skin, followed by isolation or detection of the nucleic acid from the skin sample. Applicants respectfully submit that the disclosure provides

adequate support to enable one of skill in the art to detect all nucleic acids present in the skin sample obtained using invention method.

The Examiner asserts that the specification provides enablement only for detection of certain cytokines, *i.e.*, IL-4, IL-8, IL-13, iNOS and IFN-γ, in a skin sample, and states that the detection and quantitation of other nucleic acids is not supported or necessary. The Examiner also asserts that cytokines other than IL-4, IL-8, IL-13, iNOS and IFN-γ are not known to distinguish irritant contact dermatitis (ICD) from allergic contact dermatitis (ACD). However, the claims do not specifically recite a method of distinguishing ICD from ACD. Rather, the claims recite a method of obtaining a skin sample to use for isolating and detecting nucleic acids in the skin sample. Invention methods can be used whenever obtaining a skin sample by a non-invasive method for isolating or detecting nucleic acids is desired to achieve a variety of medical and scientific goals. For example, the disclosure demonstrates that invention methods can be used to determine the presence of one or more cytokine-encoding nucleic acids, *i.e.*, a specific nucleic acid profile, thereby distinguishing ICD from ACD.

Invention methods can also be used to obtain a nucleic acid sample from skin for a different purpose, that is, a nucleic acid profile wherein the nucleic acids encode polypeptides that are not cytokines. All embodiments of invention methods need not be provided. Indeed, the U.S. Court of Customs and Patent Appeals stated that, "there is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated'." (*In re Borkowski and Van Venrooy*, 164 USPQ 642, 646 (C.C.P.A., 1970)). Therefore, the disclosure, enabling for obtaining and detecting nucleic acids encoding the cytokines IL-4, IL-8, IL-13, iNOS and IFN-γ, is also enabling for obtaining and detecting a different set of nucleic acids.

Although the disclosure need not present examples wherein further nucleic acids are obtained and detected, Applicant provides factual evidence demonstrating that the disclosure enables the

claimed invention in Declaration by Inventors under 37 C.F.R. § 1.132, submitted herewith. The Declaration demonstrates that a gene for glyceraldehyde-3- phosphate dehydrogenase (GAPDH) can be detected in skin samples obtained using invention methods. The GAPDH gene, is a "house-keeping gene" encoding a protein that is entirely unrelated to genes encoding cytokines or to genes that indicate an inflammatory profile, or to genes that distinguish between ICD and ACD. Thus, invention methods clearly are enabling for both cytokine and non-cytokine genes.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 65 to 94 and 104 to 136 under 35 U.S.C. § 112, first paragraph.

The rejection of claims 66 to 69 and 104 to 115 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed.

Applicants respectfully disagree with the Examiner's assertion that there is no guidance as to the number of times tape stripping can be performed while maintaining the non-invasive character of invention method. Those of skill in the art will readily know how many times tape stripping can be performed without causing an inflammation reaction. However, in order to expedite prosecution and reduce the issues on appeal, claims 64 and 104, and claims dependent therefrom have been amended to recite a non-invasive method for obtaining a skin sample for use in isolating or detecting a nucleic acid in a skin sample wherein the method includes applying at least one application of an adhesive to the skin in a manner such that the application does not affect the skin nucleic acid profile. Support for the amendment is found in Example 1 (at page 18, lines 8 to 10) where it is stated that the "process of tape stripping itself does not affect the skin cytokine profile during the first few hours after the procedure is done".

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 66 to 69 and 104 to 115 under 35 U.S.C. § 112, first paragraph.

Claim Rejections Under 35 U.S.C. § 102

The rejection of claims 64, 65, 70 to 82, 85 to 91 and 95 to 101 under 35 U.S.C. § 102 as allegedly being anticipated by Nickoloff and Naidu ((1994) *J. Am. Acad. Dermatol.*, 30:535-546) is respectfully traversed.

Applicants' invention methods are directed to a non-invasive method of obtaining a skin sample containing nucleic acid. The method, as described by amended claim 64 and claims dependent therefrom, includes applying and removing at least one application of an adhesive surface to the skin such that nucleic acid adheres to the adhesive surface after its removal from the skin and in a manner such that the adhesive application does not affect the skin nucleic acid profile. Invention methods are designed to obtain a skin sample without causing an inflammatory response in the skin cells. In fact, tape stripping, as performed by the method of the invention does not affect the skin cytokine profile and no inflammatory cells migrate from the circulation into the dermis or epidermis during the first few hours after the procedure is performed (Specification, page 18, lines 8 to 11).

In contrast, Nickoloff and Naidu disclose using "tape-stripping" to cause epidermal hyperplasia, *i.e.*, irritation to the skin, following which skin specimens are collected by punch biopsy. An invasive procedure such as a punch biopsy typically requires the removal of a small cylinder-shaped piece of tissue and when a large skin sample is obtained by punch biopsy, the area may need to be closed with stitches. Thus, the tape-stripping procedure used in Nickoloff and Naidu is specifically designed to cause an inflammatory reaction that is exacerbated by the performance of a punch biopsy and possibly stitches. Once the tape strips are used to cause irritation to the skin, the tape strips are discarded and have no analytical role in the study. Nickoloff and Naidu do not disclose or suggest using tape-stripping to obtain skin samples. Indeed, by following their tape-stripping procedure with a punch biopsy procedure to obtain skin specimens, Nickoloff and Naidu teach away from obtaining skin samples using tape or any other adhesive surface. Therefore, Nickoloff and Naidu cannot

anticipate Applicants' invention. Accordingly, reconsideration and withdrawal of the rejection of claims 64, 65, 70 to 82, 85 to 91 and 95 to 101 under 35 U.S.C. § 102 is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103

The rejection of claims 64 to 65, 70 to 74, 76 to 82, 85 to 91, 93, 96 to 101 and 103 under 35 U.S.C. § 103(a) as being allegedly obvious over Molen *et al.* (van der Molen *et al.* (1997) *Arch. Dermatol. Res.* 289:514-518, (hereinafter "van der Molen") in view of Kondo *et al.*(1994) L*ymphokine Cytokine Res*, 13:367-375, hereinafter "Kondo") is respectfully traversed.

Applicants' invention is directed to a non-invasive method for obtaining a skin sample from which nucleic acid can be isolated or detected. The method includes applying and removing at least one application of an adhesive to the skin such that a skin sample adheres to the adhesive after its removal from the skin.

In contrast, van der Molen discloses a study related to the kinetics and penetration depth of drugs wherein tape stripping is used to remove skin cells so that the skin remaining subsequent to tape stripping can be examined using morphological and histological methods. As many as 40 rounds of tape stripping are performed (Abstract) which is likely to result in an invasive, inflammatory response. The tape strips obtained in van der Molen were examined using X-ray microanalysis for the sole purpose of determining the distribution of skin over the tape surface in order to assess the efficacy of tape-stripping in removing skin from skin furrows. Van der Molen does not disclose or suggest using tape-stripping to obtain skin samples that can be used for isolation or detection of nucleic acids. Moreover, van der Molen does not disclose or suggest using the skin samples obtained by tape-stripping for any purpose other than evaluating the distribution of a marker compound in the skin. Accordingly, van der Molen does not disclose or suggest Applicants' invention.

The deficiencies of van der Molen can not be remedied by further reliance on Kondo. Kondo discloses a cytokine profile in mouse ear epidermis following allergic and irritating stimuli. In Kondo, epidermis samples are obtained following animal sacrifice by dissecting the animal ears away from the animal and incubating the ears with enzyme solution for 24 hours at 4°C, after which the epidermal sheet can be peeled from the ears (page 368, column 2). Thus, Kondo discloses a tedious and invasive procedure requiring the death of the subject to obtain skin samples. Kondo does not disclose or suggest using a non-invasive method to obtain skin specimens. Accordingly, Kondo does not disclose or suggest Applicants' invention.

Kondo does not remedy the failures of van der Molen and van der Molen does not remedy the failures of Kondo to disclose or suggest Applicants' claimed non-invasive methods. Indeed, the references may not be combined because the proposed modification to the prior art renders the prior art unsatisfactory for its intended purpose. (*In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984; quoted in MPEP § 214301: "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."). The tape strips obtained by van der Molen were examined by X-ray microanalysis in combination with scanning electron microscopy (SEM) (van der Molen, page 515, column b, third paragraph). These histological techniques require that the tape strips with adhering cells be cut to size, and coated with carbon for x-ray analysis, followed by sputter-coating in gold for analysis by SEM. Such treatment of the tape strips, designed to preserve the morphological features of the cells, is incompatible with molecular methods for isolating or detecting nucleic acids in the cells. Thus, the combination of the prior art references renders the prior art method unsatisfactory for its intended purpose and therefore, the references may not be combined.

Moreover, neither van der Molen nor Kondo provides any suggestion or motivation to combine the respective references. van der Molen discloses tape stripping as a means of obtaining cells only for the purpose of histological analysis. No molecular analysis, *e.g.*, detection or

quantitation of nucleic acids in skin cells, is disclosed or suggested. Kondo discloses analysis of nucleic acids in skin samples that are collected by an invasive procedure requiring the sacrifice of the subject animal. Kondo does not disclose or suggest any other means of collecting skin samples.

Accordingly, Applicants respectfully submit that neither van der Molen, nor Kondo, either separately or taken together, renders obvious the present invention. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

In the event any matters remain to be resolved in view of this communication, Examiner is requested to telephone Lisa A. Haile, J.D., Ph.D. at (858) 677-1456, or the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosures: Exhibits A and B
Declaration Under 37 C.R.F. § 1.132

EXHIBIT A: CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

64. (Amended) A non-invasive method for obtaining a skin sample for use in isolating or detecting a nucleic acid in a skin sample, the method comprising:

(a) applying at least one application of an adhesive to the skin and removing the adhesive from the skin in a manner such that the skin nucleic acid profile prior to application and after application is not affected and such that a sample comprising a nucleic acid adheres to the adhesive after its removal, or, scraping the skin with an instrument to remove a sample comprising a nucleic acid from the skin, thereby obtaining a skin sample comprising a nucleic acid; and

(b) isolating or detecting the nucleic acid from the skin sample of step (a).

104. (Amended) A non-invasive method for obtaining a skin sample for use in isolating or detecting nucleic acid encoding a cytokine in the skin sample, the method comprising:

applying at least one application of an adhesive surface to the skin and removing the adhesive surface from the skin such that a skin sample comprising nucleic acid in an amount sufficient for subsequent isolation or detection adheres to the adhesive surface after its removal and in a manner such that the skin nucleic acid profile prior to application and after application is not affected, thereby obtaining a skin sample for use in isolating or detecting a nucleic acid in a skin sample.

123. (Amended) The method of claim [121]122, wherein the cytokine is interleukin-1 (IL-l), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-10 (IL-I0), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-14 (IL-14), granulocyte macrophage colony stimulating factor (GM-CSF), or an interferon or any combination thereof.

124. (Amended) The method of claim [120]121, wherein the cytokine is an inflammatory mediator.